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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Luis De Taboada et al.	Group Art Unit 3735
Appl. No.	:	10/682,379	
Filed	:	October 9, 2003	
For	:	DEVICE AND METHOD FOR PROVIDING PHOTOTHERAPY TO THE BRAIN	
Examiner	:	David M. Shay	

DECLARATION OF LUIS DE TABOADA PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Luis De Taboada, declare as follows:

1. I am a co-inventor of the claimed subject matter of the above-captioned patent application.

2. I have reviewed the above-captioned patent application, including: the specification and figures, the as-filed claims, and the pending claims as amended in the "Amendment and Response to February 23, 2006 Final Office Action" submitted herewith. I have also reviewed the February 23, 2006 Final Office Action in the above-captioned patent application, and the prior art references cited therein, including:

U.S. Patent No. 5,150,704 issued to Tatebayashi et al. ("Tatebayashi");
U.S. Patent No. 5,282,797 issued to Chess ("Chess");
U.S. Patent No. 6,537,304 issued to Oron ("Oron");
U.S. Patent No. 6,312,451 issued to Streeter ("Streeter");
U.S. Patent No. 5,474,528 issued to Meserol ("Meserol");
U.S. Patent No. 5,622,168 issued to Keusch et al. ("Keusch").
U.S. Patent No. 5,643,334 issued to Eckhouse et al. ("Eckhouse");
U.S. Patent No. 6,045,575 issued to Rosen et al. ("Rosen");
U.S. Patent No. 6,277,974 issued to Lo et al. ("Lo"); and

U.S. Patent No. 6,551,308 issued to Mueller et al. ("Mueller").

3. Tatebayashi discloses a laser therapeutic apparatus for treating a patient by irradiating selected body parts by laser beams from a plurality of laser probes. Tatebayashi discloses irradiating various body parts (*e.g.*, finger joints, toe joints, and joints such as the shoulders, knees, wrists, ankles), but does not disclose or suggest irradiating the brain. In addition, while Tatebayashi discloses using laser diodes to generate the laser light, Tatebayashi does not disclose or suggest any values of the power density or the wavelength with which the body parts are irradiated. Persons skilled in the art of phototherapy would understand the disclosure of Tatebayashi as not disclosing or suggesting irradiating a portion of the patient's brain approximately 2 centimeters below the dura with light having a power density between about 0.01 mW per square centimeter and about 100 mW per square centimeter.

4. Chess discloses a method of treating cutaneous vascular lesions (*e.g.*, vericose veins) by laser irradiation. Chess discloses irradiating the target area through the epidermis while simultaneously subjecting the epidermis to a cooling medium at the location of the epidermis entered by the laser beam. Chess does not disclose or suggest irradiation of the brain or any values of the power density of the irradiation. Persons skilled in the art of phototherapy would understand the disclosure of Chess as not disclosing or suggesting irradiating a portion of the patient's brain approximately 2 centimeters below the dura with light having a power density between about 0.01 mW per square centimeter and about 100 mW per square centimeter.

5. At column 5, line 6 - column 6, line 15, Oron discloses phototherapy experiments that were performed on rats, and discloses that energy densities of 8 mW per square centimeter or of 5 mW per square centimeter reached the brain tissue of the rats. A rat brain is typically only about 10 to 12 millimeters in diameter, so no portion of the rat brain is at a depth of approximately 2 centimeters below the dura of the rat brain. In addition, it is not obvious that irradiation of the surface of a rat brain would have a corresponding effect if performed on a human brain. Persons skilled in the art of phototherapy would understand the disclosure of Oron as not disclosing or suggesting irradiating a portion of a brain with light having a power density between about 0.01 mW per square centimeter and about 100 mW per square centimeter at a depth of approximately 2 centimeters below the dura.

6. At column 6, lines 17-39, Oron also discloses measurements of the penetration of laser irradiation through a fresh human skull to illustrate the transmittance of light through the skull wall. Oron discloses that the beam diameter of the laser was dispersed from 2 millimeters

externally to the skull to 3.5 centimeters in the skull cavity and had a power density of 3 mW per square centimeter after penetration through a skull wall having a thickness of about 8 millimeters. Oron is silent regarding whether these measurements were made after the brain was removed from the skull or whether the brain remained in the skull during these measurements and was irradiated. Oron is also silent regarding the irradiation of the brain with light at a point approximately 2 centimeters below the dura. Persons skilled in the art of phototherapy would understand from the disclosure of Oron that Oron does not disclose or suggest irradiating a portion of the brain approximately 2 centimeters below the dura with light having a power density between about 0.01 mW per square centimeter and about 100 mW per square centimeter.

7. Streeter discloses a low level laser therapy apparatus for treating musculoskeletal injuries, improving local cardiac microcirculation, and treating spinal cord transection. Streeter does not disclose or suggest irradiation of the brain or any values of the power density of the irradiation. Persons skilled in the art of phototherapy would understand the disclosure of Streeter as not disclosing or suggesting irradiating a portion of the patient's brain approximately 2 centimeters below the dura with light having a power density between about 0.01 mW per square centimeter and about 100 mW per square centimeter.

8. The irradiation of a portion of the brain approximately 2 centimeters below the dura with a power density between about 0.01 mW per square centimeter and about 100 mW per square centimeter provides substantial advantages that were unexpected in view of previous work. For example, Exhibit A presents data from a recently-completed effectiveness and safety trial (unpublished) of a therapy apparatus and method in accordance with certain embodiments of the present application. This trial evaluated the effectiveness and safety of a treatment regiment which included removing hair from the subject's scalp, followed by application of radiation having a wavelength of 808 nanometers and a nominal power density of about 700 mW per square centimeter on 20 pre-determined locations on the scalp for two minutes on each site.

9. Exhibit A shows the scores on the mean NIHSS outcome scale over time for an "active" group of subjects that received the radiation treatment and a "control" group of subjects that received a placebo or sham treatment. Exhibit A shows that statistically significant differences in mean NIHSS scores between treatment groups appeared soon after treatment and were apparent throughout the 90-day study period. In addition, this study found that the active group exhibited more improvement as measured on various other outcome scales (*e.g.*, bNIH,

mRS, Rankin, BI, GS) than did the control group over the course of the study. Thus, subjects who received active treatment had better outcomes than did subjects who received sham control treatments.

10. In a pair of separate studies, the transmission of radiation through a cadaver human skull and through a cadaver human brain was measured. In the skull transmission study (V.V. Lychagov *et al.*, "*Experimental study of NIR transmittance of the human skull*," Complex Dynamics and Fluctuations in Biomedical Photonics III, ed. by V.V. Tuchin, Proc. of SPIE Vol. 6085, 6085T (2006), attached herewith as Exhibit B), an input beam having a wavelength of 810 nm, a power density of about 68 mW per square centimeter, and a beam diameter of about 30 millimeters was applied to the shaved skin of the skulls of 20 cadavers at five regions with various thicknesses. Figure 2 of Exhibit B illustrates that the transmittance of the light varied from 0.5% to 5%, depending on the thickness of the irradiated portion of the skull. We performed an independent measurement (unpublished) of the transmission of 808-nm light with a power density of 424 mW per square centimeter applied to a cadaver human skull (including the shaved skin) having an average thickness of about 11 millimeters, and calculated the overall transmittance of the skull tissues to be about 2%, which agrees well with the results of Exhibit B.

11. In the brain transmission study (unpublished), for an input beam having a wavelength of 808 nm, a power density of 10 to 20 milliwatts per square centimeter applied directly to the dura, and a beam diameter ($1/e^2$) of 30 millimeters at the dura, the power density at a depth of 15 millimeters from the dura was measured to be 0.148 mW per square centimeter, and at a depth of 25 millimeters from the dura was measured to be 0.020 mW per square centimeter.

12. The effectiveness and safety trial cited above applied 808-nm light having a nominal power density of about 700 mW per square centimeter to the shaved scalps of the trial subjects. Using a value of 2% transmittance, in agreement with the skull transmission study cited above, the power density applied to the dura of the trial subjects was about 14 mW per square centimeter. Further using the data from the brain transmission study cited above, the effectiveness and safety trial cited above therefore included irradiating a portion of the brain approximately 2 centimeters below the dura with a power density between about 0.01 mW per square centimeter and about 100 mW per square centimeter.

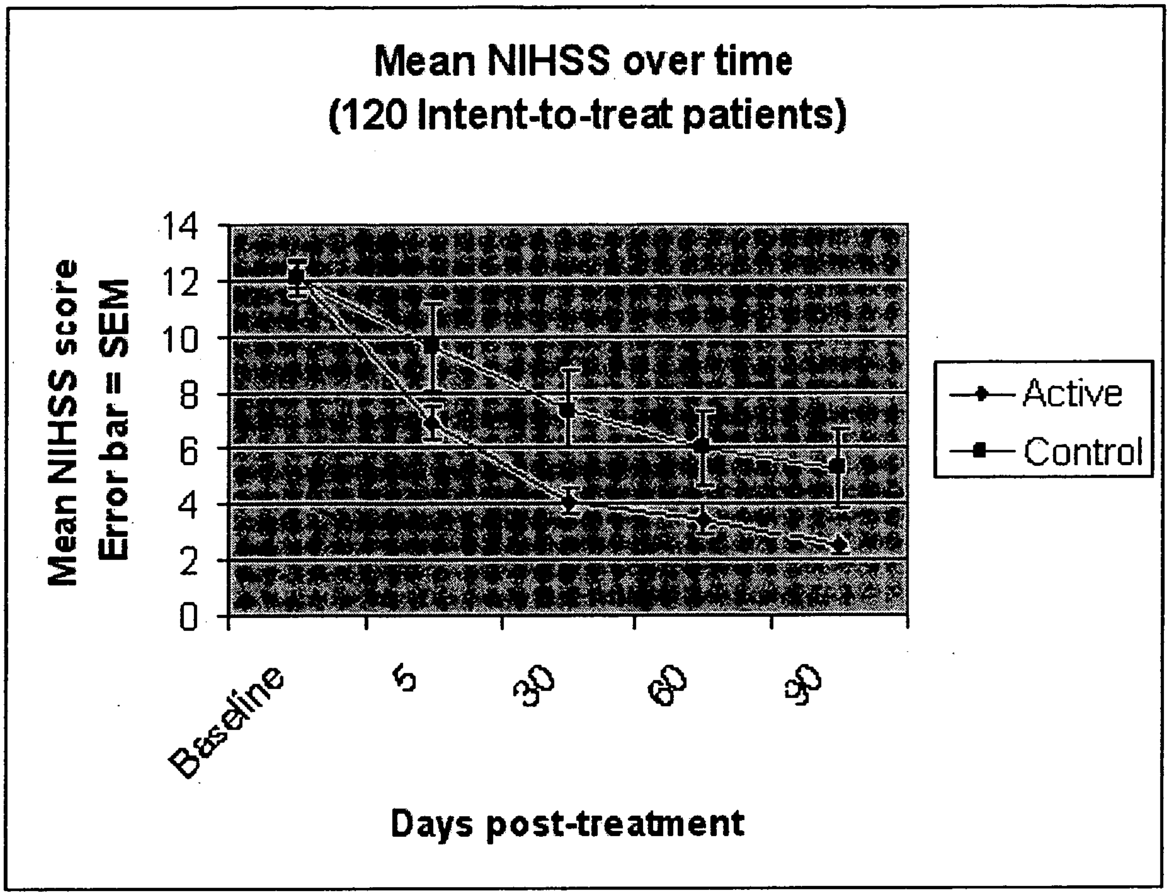
13. Therefore, the experimental results of the effectiveness and safety trial cited above are evidence that irradiation of a portion of the brain 2 centimeters below the dura with a power

density between about 0.01 mW per square centimeter and about 100 mW per square centimeter provides substantial benefits that were unexpected in view of prior work.

14. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001, Title 18 of the United States Code, and that willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: August 18th, 2006 By: Luis De Taboada
Luis De Taboada

Exhibit A:



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Experimental study of NIR transmittance of the human skull

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ABSTRACT

The results of measurements of transmittance of high power laser irradiation through skull bones and scalp are presented. Dependences of transmittance on sample thickness were received. Character of transmittance was investigated and characteristics of heterogeneity of the scattering structure of the skull bones are proposed. Besides that, variation of temperature of skull and scalp surfaces under exposure of high power laser irradiation during experiments was controlled. Experimental results were verified by Monte-Carlo simulations.

Keywords: transmittance, bone structure, laser therapy, Monte-Carlo simulation

1. INTRODUCTION

During the last years laser technique had found increasingly wide application in medicine. In addition to using of high-power lasers in surgery (laser scalpel) laser irradiation is widely used in therapy. There are a lot of fields of application of laser therapy, such as: cure of arthritis, oculars, cardiac, skins and blood diseases. The influence of different types of laser systems on different biological objects was investigated during this time.

Laser therapy at present is one of the most effective methods of treatment and prophylaxis of various diseases, primarily owing to possibility of fine adjustment of biological processes and noninvasive influence on structure of biological tissues. However, it is necessary to define properly radiation dose to avoid of negative thermal effect on biological tissues. As is well known, the power density of laser irradiation within the range of from 0.1 to 10 mW/cm2 is had the most effective influence to human tissues. The lower power density of laser irradiation could exert just stimulation therapy; the abnormal changes in tissues could happen using the high value of power density of laser irradiation.

One of the possible adaptations of this method is a therapy of stroke and infarcts. Accordingly, the main aim of our studies was estimation of a dose of laser irradiation transmitted through skull bones and scalp tissue and arrived at a brain. A lot of parameters are significant in this case such as wavelength and power of irradiation, geometry of a beam, and mode of irradiation (continues wave, pulsed beam). To understand the adaptation processes within bone tissue it is not only necessary to take into consideration bone density but also bone structure.

2. EXPERIMENTS

Experimental research was carried out with preparing bone tissue and skin of the head. The scheme of the experimental setup is presented in Figure 1a. Collimated, 810 nm, 1 Watt laser beam of approximately 30 mm in diameter was used as a light source.

CCD camera with necessary neutral filters was used for obtaining of a pattern of spatial distribution of transmitted irradiation.

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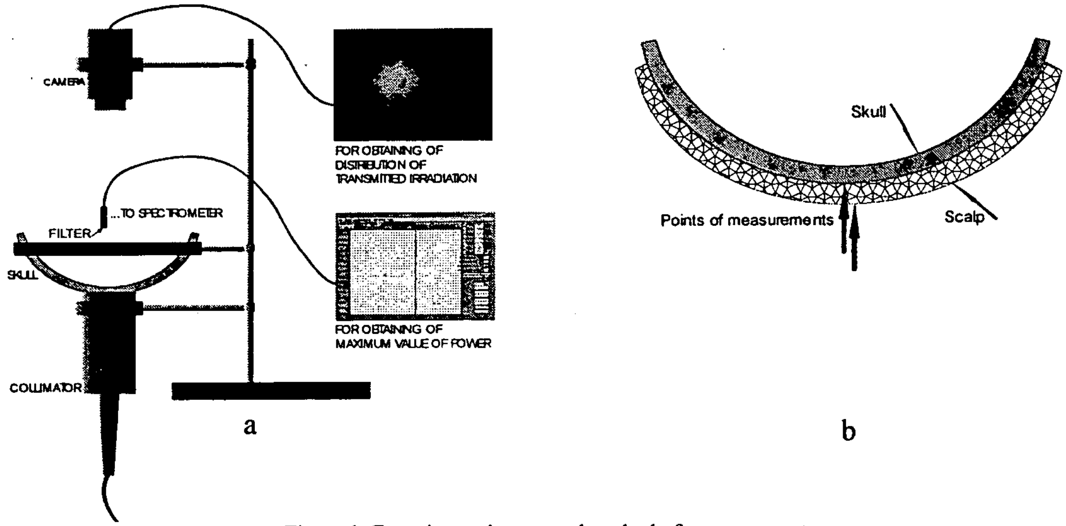


Figure 1: Experimental setup and method of measurements

The absolute value of power at the central of distribution (maximum power) was measured using a 1 mm diameter fiber with cosine corrector and an Ocean Optics a USB2000 spectrophotometer. Thickness of the sample was measured at five points with the help of the slide gauge and averaged. The skin samples were held between two object-plates during measurement. Temperature of samples was measured by the voltmeter V7-27A/1 with the contact probe for temperature detection (Fig. 1b). Square of working substance of the probe is equal to 1 square millimeter. Temperature was measured at the skin surface and skull in the center of irradiated field after exposure.

3. MEASUREMENTS

Using CCD we made a sequence of frames (25 frames) with each domain of interest (temples, forehead, occiput, and vertex) for averaging, sequence of frames with the laser switch off for subtraction of backgrounds, and one frame with the scale for calculation of real dimensions of the frames. Then maximum power in the center of the distribution was measured five times by the spectrometer, using available calibration, and the light distribution was normalized to mean value. The resulting power density distribution was calculated in the following way:

$$Pdistr_{res} = \left(\frac{Pdistr_1 + Pdistr_i + ... + Pdistr_{25}}{25} - \frac{Pbackgnd_1 + ... + Pbackgnd_{25}}{25} \right) \cdot \frac{(P\max 1 + ... + P\max 5)}{5 Pdistr\max}$$

The same procedure as described above was realized both with the skull only and with the skull with shaved scalp. After measurements we calculated the main characteristics of light transmittance: average radius of light distribution with the fixed power density, and its standard deviation. For example:

$$R_{0.7\max} = \frac{\sum_{n=1}^{N} R_{An}}{N},$$

where An is a point from vicinity of 0.7MaxPower level (0.7-ε; 0.7+ε), and R_{An} is a radius vector of this point on the assumption of $A0$ is a center of coordinate. N – amount of this points. Analogously for $R_{0.5}$ and $R_{0.1}$.

4. RESULTS AND CONCLUSIONS

Measurements were carried out on 20 cadaver's heads, at 5 domains: forehead, left and right temples, occiput and vertex. In such a way dependence of transmittance on sample thickness was build up on 100 points. Measurements were performed both on the skull with shaved scalp and on the separate skull. In Figure 2 dependence of transmittance on sample thickness for both cases is presented.

As it can be seen from this picture, decrease of transmittance with increase of sample thickness can be approximated well by exponential decay. The value of transmittance is varied from 0.5% to 5% in case of sample with scalp and from 1% to 16% in case of single skull. In consequence of input power density was 68 mW/cm^2 value of transmitted power density varied from 340 μW/cm^2 to 3400 μW/cm^2 and from 680 μW/cm^2 to 9000 μW/cm^2 respectively. It is evident from results of experiments with separated bone tissue and experiments with skull and scalp, that layer of skin influences on transmittance the same way as skull, with that thickness of skin layer is less than thickness of skull. Such experimental results comply well with theoretical Monte-Carlo simulations, results of which are presented in Figure 3. It is obvious from this picture, that the theoretical dependence of transmittance on sample thickness has the same decay rate as experimental curve. Distinctions of the theoretical values of transmittance of skull-scalp sample from experimental data can be explained by that average optical parameters were used in Monte-Carlo simulations.

Temperature control was provided during experiments. Temperature of the skin surface rose on 4 °C on average for the time of exposure of 4 minutes and the temperature of the external surface of the skull rose on 2 °C on average for the same time of exposure under such power of irradiation. Negligible changes of the temperature of the internal surface of the skull in few percent of degree were notice. It can be referred to inaccuracy of measurements. Dependence of temperature on time of exposure for one of the samples is represented in Table 1.

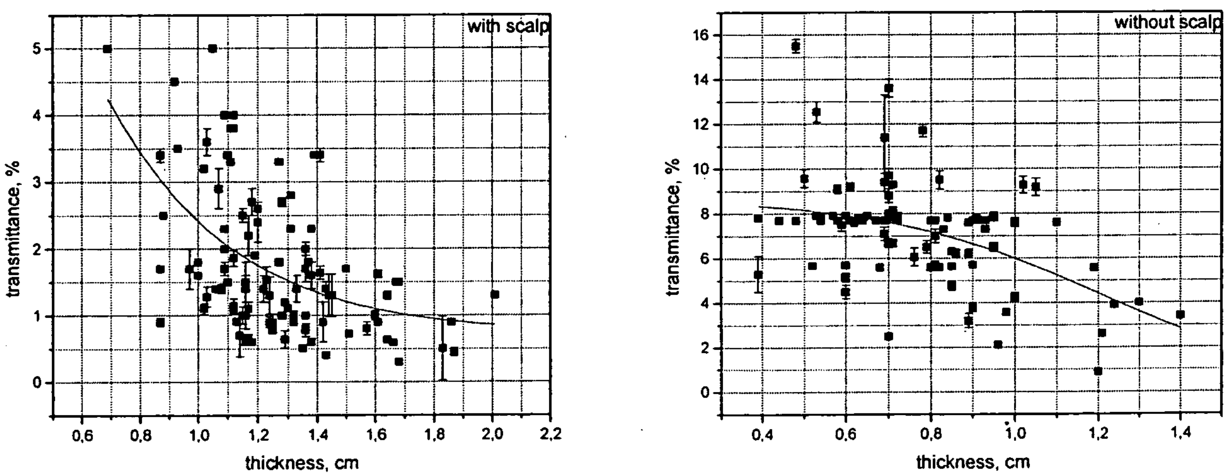
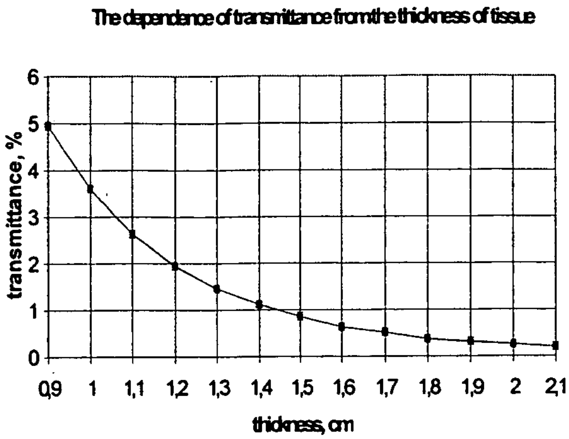


Figure 2: Dependence of transmittance on thickness of the sample – experimental results

It was said above, that the radii of equal power density (0.1, 0.5 and 0.7 of maximum value) were estimated for the distributions of power density obtained in experiments. The dependences of radius 0.5 of maximum on transmittance are presented in Figure 4. It follows from this figure, that increasing of radius 0.5maximum with increasing of transmittance is well seen in most cases. Besides that, standard deviation of each radius of fixed power density was calculated, which defined, in this case, degree of heterogeneity of tissue's transmittance related with the features of the tissue structure, mainly with the features of the bone tissue.

We can suppose that this scheme of irradiation can be used for therapeutic irradiation and can be employed for clinical study on the assumption of expected therapeutic power density at the *dura mater* of 7.5 mW/cm^2. Values of power density obtained in both experiment and simulation lie in this limit.



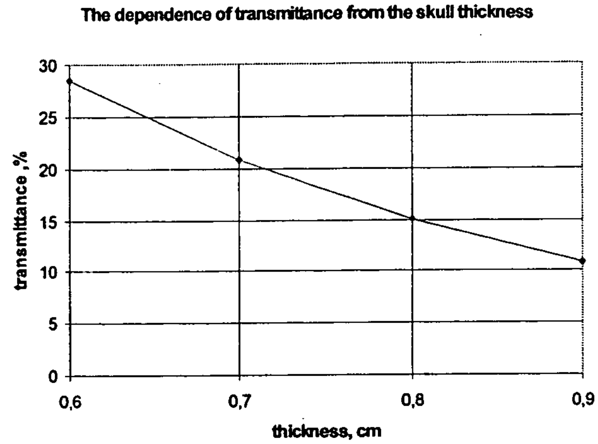
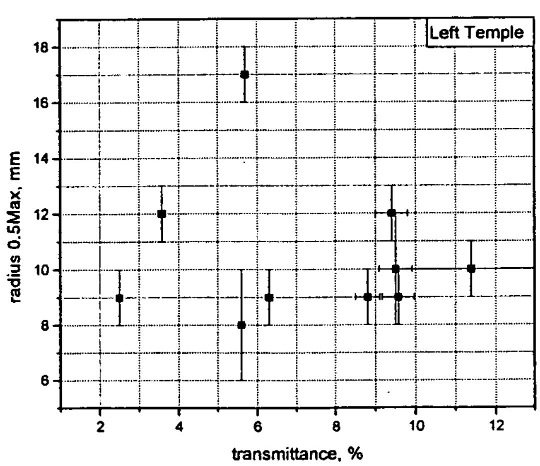


Figure 3: Dependence of transmittance on thickness of sample – Monte-Carlo simulations

Table 1: Dependence of temperature on time of exposure		
object	time of irradiation, min	temperature, °C
skull	1	21.9
scalp	1	22.0
skull	2	22.6
scalp	2	23.2
skull	3	24.1
scalp	3	24.6
skull	4	24.8
scalp	4	25.6



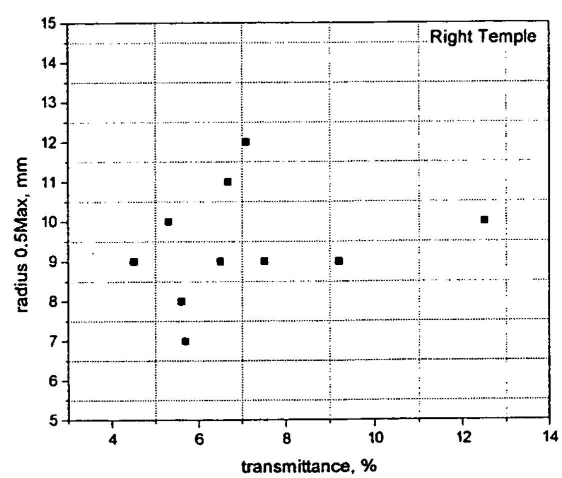


Figure 4: Dependences of radius 0.5 of maximum on transmittance

ACKNOWLEDGEMENTS

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REFERENCES

1. Stefan Tauber, Reinhold Baumgartner, Karin Schorn, and Wolfgan Beyer, "Lightdosimetric Quantitative Analysis of the Human Petrous Bone: Experimental Study for Laser Irradiaton of the Cochlea," *Lasers in Surgey and Medicine* **28**, pp. 18-26, 2001.
2. N. Ugryumova, S.J. Matcher, D.P. Attenburrow, "Measurement of bone mineral density via light scattering," *Phys. Med. Biol.* **49**, pp. 469-483, 2004.
3. T.L. Troy, S.N. Thendnadil "Optical properties of human skin in the near infrared wavelength range of 1000 to 2200 nm," *JBO* **6**(2), pp. 167-176, 2001.
4. P.I. Begun, U.A. Shukeylo, *Biomechanics*, Politechnika, 2000, Saint-Petersburg.
5. V. V. Tuchin(Ed.), *Handbook of optical biomedical diagnostics,* SPIE Press, **PM107**, 2002, Bellingham.
6. S. Stolik, J.A. Delgado, A. Perez, L. Anasagasti "Measurements of the penetration depths of red and near infrared light in human "ex vivo" tissues" *J. of Photochemistry and Photobiology B: Biology* **57**, pp. 90-93, 2000.
7. M. Firbank, M. Hiraoka, M. Essenpreis and D.T.Delby "Measurements of optical properties of the skull in the wavelength range 650-950 nm" *Phys. Med. Biol.* **38**, pp. 503-510, 1993.